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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Thomas F. MEYER et al

Serial No.: 09/284,233

Filed: April 12, 1999

For: HELICOBACTER PYLORI LIVE VACCINE

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner
for Patents
Washington, DC 20231

June 8, 1999

Sir:

In compliance with applicant's duty of disclosure under 37 CFR 1.56, enclosed are copies of material information of which applicant is aware, and which may be relevant to the above-identified application.

We have been advised that the applicants' German patent attorneys have conducted an extensive search to identify references relevant to the present application. The German patent attorneys furnished us with the following comments:

WO 94/24291
discloses attenuated Salmonella cells serving as a carrier for a heterologous antigen, for example, antigenic determinants from Plasmodium. In particular, the antigen is a fusion protein from hepatitis B virus core antigen and an antigenic determinant from Plasmodium (cf. claims 1 and 2). No Helicobacter antigens are disclosed.

U.S. 5,811,105
relates to a vaccine comprising a pharmaceutically acceptable carrier and an attenuated bacterium, wherein attenuation is effected by mutations in two discrete aro genes. The bacterium can be a Salmonella bacterium. No Helicobacter antigens are disclosed.

EP 0 863 211 A1
describes a fusion protein and a vaccine composition comprising said fusion protein or an attenuated cell expressing said fusion protein. The attenuated cell may be Salmonella. The fusion protein consists of a first immunogenic polypeptide which is used as an adjuvant, particularly tetanus toxin fragment C, and a second polypeptide fusioned thereto, against which an immune response is to be elicited. On page 3, lines 8-24 a great number of such second polypeptides is identified, however, there are no Helicobacter antigens.

WO 97/12909
relates to novel membrane proteins from Helicobacter pylori but does not include any indication of a live vaccine, wherein a recombinant, attenuated microbial pathogen expresses a Helicobacter antigen. The application discloses the treatment or prevention of a Helicobacter infection by administration of a subunit vaccine comprising isolated proteins (cf. page 9, lines 33 to page 10, line 12).

WO 86/01829
refers to a method of preparing an avirulent strain of a microbial pathogen and to a vaccine containing a corresponding strain. This document does not disclose any hint that a thus attenuated strain could be used as a carrier for a heterologous antigen, and there is no hint at Helicobacter antigens.

WO 97/14782
was published after the priority date of the present application and concerns live attenuated vaccine strains against gram-negative enteric pathogens which have a deficiency in expressing homologous O-PS and the capability of expressing heterologous O-PS covalently coupled to the LPS core. The expression products of said genes, however, would be located inside the cell and thus would not qualify for a heterologous antigen. Helicobacter pylori is mentioned as an enteric pathogen in the first paragraph of page 2, however, no live vaccine expressing a heterologous Helicobacter antigen is mentioned. On the contrary, it is suggested on page 14, last paragraph, to use the Helicobacter strain modified according to this document as a vaccine strain.

U.S. 5,583,038
discloses a recombinant mycobacterium transformed with DNA encoding a polypeptide, said polypeptide comprising a lipoprotein secretion signal sequence and a heterologous antigen. The antigens are derived from Borrelia burgdorferi, and there is no indication of Helicobacter antigens.

WO 86/03123
is concerned with live vaccines and, in particular, Salmonella exhibiting two non-reverting auxotrophic mutations. These vaccines may also be used as carriers for heterologous antigens. On page 17, line 30 to page 19, line 23 a multitude of suitable antigens and corresponding organisms are listed,

however, Helicobacter is not mentioned.

WO 96/14087
relates to a method of inducing an immune response to a tumor-specific antigen. This document does not include any indication of an attenuated microbial pathogen as carrier nor of a Helicobacter antigen.

WO 95/20665
discloses a vaccine composition comprising an attenuated bacterium and a pharmaceutically acceptable carrier. The attenuated bacterium comprises a DNA sequence under the control of an in vivo inducible promoter (the htrA promoter) which codes for one or several heterologous proteins. No Helicobacter antigens are disclosed.

WO 96/10421
pertains to a vaccine composition comprising influenza virus antigens and a mucosal adjuvant, namely chitosan. No Helicobacter antigens or live vaccines are disclosed.

WO 94/19482
is concerned with a bacterial chromosome containing a DNA sequence which encodes a heterologous antigen under the control of an iron-regulated promoter. The document discloses a cell containing said chromosome and a vaccine containing said cells. A multitude of heterologous antigens is listed on page 5, lines 4-23, but there is no indication of Helicobacter antigens.

WO 96/34624
corresponding to scientific publications Ferrero et al. (PNAS 92 (1995) 6499-6503) and GUT 37 (1995) A51, cited in Telford and Ghiara, Drugs 52: 799-804 (1996)
are concerned with a composition comprising a mixture of Helicobacter antigens consisting essentially of UreB and HspA of H.pylori, provoking a mucosal response. However, these data cannot be compared directly with the data of the present application, mainly because the recombinant antigen was administered in combination with a highly toxic adjuvant, namely cholera holotoxin. The use of these toxic adjuvants has severe disadvantages and renders the vaccine unsuitable for administration to humans.

Michetti et al. (Gastroenterology 107 (1994) 1002-1011) and Corthésy-Theulaz (Gastroenterology 109 (1995) 115-121) both use several repeated infections with recombinant H.pylori antigens (urease) in combination with cholera toxin as well as an infection with Helicobacter felis. None of these documents discloses results comparable with the results shown in the present application.

WO 94/03615 and WO 94/24291
are concerned with attenuated Salmonella strains with an inducible promoter for expressing heterologous antigens. These documents do not suggest the Helicobacter live vaccine according to the present invention. However, at the priority date of the present application, it was entirely unexpected and unpredictable that the live vaccine approach by recombinant Salmonella would lead to protection against Helicobacter. Thus, it becomes clear that the prior art on the priority date of the present application did not give a skilled artisan a clear and definite hint as to the subject matter of the present application but, due to the special characteristics of Helicobacter, even led him away from the subject matter of the present application. This is also supported by the documents

Eaton and Krakowka (Gastroenterology) 103 (1992) 1580-1586) and Lee and Buck (Alimentary Pharmacology and Therapeutics 10 (1996) Suppl.1: 129-138)
Eaton and Krakowka show that oral vaccination with H.pylori cannot prevent subsequent infection with viable H.pylori pathogens. Lee and Buck, again, describe the problems of the toxic mucosal adjuvants used in the prior art in the case of application in humans.

Developments Biol.Stand.84 (1995) 211-219 gives no instructions how to develop an efficacious recombinant bacterial live vaccine against H.pylori, but refers generally to the history of live bacterial vaccines.

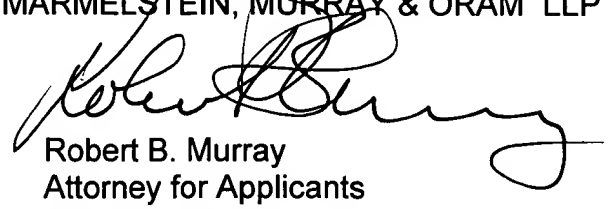
The majority of these additionally identified documents describes recombinant live vaccines, among others also attenuated Salmonella carrier cells expressing heterologous antigens. The expression of Helicobacter antigens in an attenuated microbial pathogen is neither disclosed nor rendered obvious by these prior art documents.

It should be noted that the undersigned has not made an independent review of the attached references to determine the accuracy of the German patent attorneys comments.

A copy of each reference and a PTO-1449 are attached.

In the event there are any fees due in connection with the filing of this paper, please charge our Deposit Account No. 14-1060

Respectfully submitted,
NIKAIDO, MARMELSTEIN, MURRAY & ORAM LLP



Robert B. Murray
Attorney for Applicants
Reg. No. 22,980

Atty. Case No. P564-9008
Metropolitan Square
655 Fifteenth Street, N.W.
G Street Lobby - Suite 330
Washington, D.C. 20005-5701
RBM/cb
Enclosure: References (21)
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